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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,492	01/10/2001	Svetlana Dolina	1067/2	1483

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EXAMINER	
CHERNYSHEV, OLGA N	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,492	DOLINA ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 67-93 is/are pending in the application.

4a) Of the above claim(s) 72 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 67-71 and 73-93 is/are rejected.

7)☒ Claim(s) 91 is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Status of the claims

1. Claims 1-15 have been cancelled and claims 67-93 have been added as requested in the amendment of Paper#8, filed September 10, 2001. Applicant is informed that among new added claims 1-28 claim 18 was missing (claim 17 is followed by claim 19). Applicant is informed that according to Rule 1.126 37 CFR newly added claims 1-28 were re-numbered as claims 67-93. Applicant is required to make appropriate corrections in the text of claims to properly identify new claims dependency.

Election/Restrictions

2. Applicant's election of invention directed to a method of diagnosing, claims 67-93 in Paper No. 8 is acknowledged. Since Applicant did not present any arguments to traverse the restriction, response to restriction requirements is considered as election without traverse. The requirement is deemed proper and is therefore made FINAL.

3. Applicant's election of species as a relationship between KA and any other kynurenine metabolite is acknowledged.

Claim 72 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Claims 67-71 and 73-93 are under examination in the instant office action.

Specification

4. There is a large blank space on page 18. Appropriate correction is required.

5. The disclosure is objected to because of the following informalities: on page 19, line 7 there is an open parenthesis; there is no period at the end of the sentence on line 14. Applicant is advised to check the specification for other possible typographic errors.

Appropriate correction is required.

6. Claim 91 is objected to because of the following informalities: it is suggested that Applicant uses consistent subnumbers for each claim presented in the specification. For example the subnumbers could be a, b, c or a), b), c) or I), ii), iii) etc. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 67-71 and 73-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The present invention, claims 67-71, 73 and 78-94, is directed to a method for diagnosing a medical condition, which comprises measuring a concentration of at least two kynurenine

metabolites in a sample and comparing said concentration with control values and a system for diagnosis. However, the instant specification does not provide any guidance or working examples on how to diagnose a medical condition by the claimed method or how to use the claimed system, thus, requiring undue experimentation for one skilled in the art in order to practice the invention as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

The state of the prior art is such that there are no references available to predict, suggest or assume a possibility of diagnosing a medical condition based on a method of measuring and comparing concentrations of kynurenine metabolites. The claims encompass a very broad invention, which is directed to diagnosis of any possibly medical condition. It is impossible to envision that diagnosis of numerous known medical conditions of different etiology and symptomology can be based just on comparison of concentration of kynurenine metabolites. The instant specification fails to provide any guidance on how to achieve the claimed method of diagnosis, or to support the invention by presentation of working examples. It is unclear how one could obtain any sample from a subject, measure concentration of kynurenine metabolites and, after comparing the results with control values or after establishing a ratio between said metabolite concentrations, provide a diagnosis of "a medical condition" in a subject. It is

unknown and undisclosed what medical conditions have been diagnosed using the claimed method, except for the limited number of examples related to epileptic conditions. It would be also impossible to expect that a system comprising a sample taken from a subject and a device to measure concentrations of kynurenine metabolites could be successfully used for diagnosis of any or every possible medical condition. Therefore, it would require undue experimentation for a skilled artisan to determine how to successfully practice the Applicant's invention as currently claimed.

8. Claims 74-77 are directed to the method for diagnosis of a medical condition when it is related to epilepsy, is epilepsy or is a predisposition of epilepsy. The instant specification discloses the results of the experimental study performed on two animal models of genetic epilepsy (seizure-naive genetically epilepsy-prone (EP) rats, rats with spontaneous non-convulsive absence seizures (GAER) and control epilepsy-resistant (ER) rats), and on plasma samples of patients with epilepsy and with pre-epileptic condition.

According to the definition and description of epilepsy, or seizure disorders, "No obvious cause [of epilepsy] can be found in about 75% of adults and a smaller percentage of children under 3. [] Convulsive seizures may be associated with a variety of cerebral or systemic disorders, as a result of a focal or generalized disturbance of cortical functions" (see The Merck Manual, 1987, pp.1366-1371, especially p. 1367, first, second and third paragraphs). Applicant supports the same account for different types of epilepsy on page 1 of the instant specification "The different types [of epilepsy] include partial (symptomatic) and generalized idiopathic seizures" (lines 11-12). Therefore, different cases epilepsy or seizures have different etiology, origin and development. The instant specification fails to describe how predictive the animal

model of rat epilepsy would be for, for example, human patients suffering from seizure disorders or from which particular forms of epilepsy. There is no evidence of record that the claimed method for diagnosis of epilepsy or predisposition to epilepsy, based on discovered difference in concentration of kynurenine metabolites of genetically epileptic rats, can be extrapolated and successfully practiced on human subjects suffering from epilepsy regardless of particular type or origin of the disorder. Moreover, as it is indicated in the instant specification "The background art neither taught nor suggested that such biochemical markers [kynurenine metabolites] were associated with epilepsy, and certainly did not teach or suggest that these markers could be used to detect a predisposition to genetic seizure disorders and/or effectiveness of AED treatment in a subject" (page 9, lines 28-31). Thus, the state of prior art of the claimed invention is unpredictable for diagnosis of epileptic disorders in general and for diagnosis based on the use of differences of kynurenine metabolites in a sample of affected subject in particular to reasonably expect the claimed method to be effective in diagnosis of seizure disorders.

The presented results of clinical study of plasma levels of kynurenines in children with Febrile Convulsions (FC), again, refer only to this special condition, which is considered as a risk factor of developing epilepsy ("7% of children with FC will have epilepsy by the age of 25 years", as stated on page 22, lines18-19 of the instant application). The discovery of the imbalance between the concentrations of neuroprotective and neurotoxic compounds in blood samples of such patients was left at the level of hypothesis because there is no data confirming how many children from the group included in the study eventually developed epilepsy. Taking into consideration the fact that epilepsy cannot be defined as a disorder of the same etiology and represents a consequence of a variety of different disorders and conditions, one cannot predict

that by measuring the parameters of kynurenine metabolism in plasma sample of a patient a diagnosis of a complicated syndrome such as epilepsy can be achieved.

Thus, in view of the lack of teachings and unpredictability of the art set forth earlier, and also the total absence of the working examples, the instant specification is not found to be enabling for a method for diagnosing a medical condition, which comprises measuring a concentration of at least two kynurenine metabolites in a sample and comparing said concentration with control values. It would require undue experimentation and making a substantial inventive contribution for the skilled artisan to discover how to use Applicants' invention as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 67-71 and 73-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 67 and 89 are indefinite because of the recitation of "corresponding reference concentrations". If this refers to control values of subjects with or without medical condition, then it is not clear how these values can be established before the diagnosis of such condition is made using the claimed method. Clarification is required.

11. Claims 84 and 88 are indefinite. The presence of (e) and (f) makes the claims confusing and indefinite because these steps are not additional steps in the claims.

12. Claims 84-87 are ambiguous and confusing because they employ a term "anti-epileptic drug" and a term "AED" to refer to the same element without indication that they are the same. Claim 84 should be changed to refer to an "anti-epileptic drug (AED)".

13. Claim 93 recites the limitation "the method" of claim 92 while the claim 92 is directed to the system for diagnosis. There is insufficient antecedent basis for this limitation in the claim.

14. Claims 68-71, 73-83 and 90-92 are indefinite for being dependent from the indefinite claims.

Conclusion

15. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-0294 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December

28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D. *OC*
November 19, 2001

JOHN ULM
PRIMARY EXAMINER
GROUP 1800